REMARKS

Claims 48 and 55-57 were rejected in the outstanding Office Action. Claim 56 is cancelled herein, and new claims 58-60 are submitted. Support for new claims 58 and 59 is found in the specification at least at page 72, lines 17-19, and support for new claim 60 is found in the specification at least at page 72, lines 19-20. Accordingly, no new matter has been added by way of the claim amendments and new claims.

Claims 48, 55, and 57 are amended herein without prejudice and without acquiescence solely to further prosecution of this case. Support for amendments to these claims is found in the specification, for example at page 10, lines 15-19 and original claims 31, 32, 45, and 46. Applicants reserve the right to pursue the material in non-amended form in subsequent prosecution. In view of the above amendment, Applicants believes the pending application is in condition for allowance.

I. Issues regarding Priority

The Examiner maintains the notion that the priority document U.S. Provisional Patent Application Serial No. 60/137,060, filed June 1, 1999, does not support the subject matter of the pending claims and alleges that the effective filing date of the instant claims is June 1, 2000 (*i.e.*, the filing date of PCT/US00/15410).

Claim 50 of the '060 priority document is directed to a composition comprising a Math1 protein or gene in combination with a delivery vehicle, wherein the delivery vehicle causes a therapeutically effective amount of Math1 to be delivered to a cell. Claim 60 of the '060 document recites, "The composition of claim 50, wherein Math1 and the receptor-binding domain of a bacterial toxin comprises a fusion protein."

The Examiner states that "it is not readily apparent that the fusion protein in claim 60 is a Math1 fusion protein or that the Math1 protein is fused with the receptor-binding domain of the bacterial toxin." The Examiner contends that "As written, it appears that the 'receptor-binding domain' of the 'bacterial toxin comprises a fusion protein.'"

Applicants disagree with the Examiner's interpretation of claim 60. The sentence does not grammatically make sense any way other than comprising a fusion protein

comprising Math 1 and the receptor-binding domain of a bacterial toxin. In this regard, the fact that the term "Math1" is ***followed by the term "and"*** indicates that the fusion protein comprises "Math1" and the receptor-binding domain of a bacterial toxin. Furthermore, if claim 60 were interpreted as suggested by the Examiner, i.e., the bacterial toxin comprises a fusion protein, then there would be no antecedent basis for the term "receptor-binding domain." Furthermore, it is not clear to Applicants what the Examiner believes the term "Math1" refers to, if not one member of a fusion protein. The claim clearly states that Math1 is in a fusion protein with the receptor-binding domain of a bacterial toxin. Thus, Applicants respectfully request that the Examiner acknowledge that the effective priority date is the filing date of U.S. Provisional Patent Application 60/137,060, *i.e.*, June 1, 1999.

Even if the '060 application does not support the pending claims, ***which Applicants assert is not the case***, the specification of the U.S. Provisional Patent Application Serial No. 60/176,993 very clearly discloses fusion proteins commensurate in scope with the pending claims (see the '993 application at, for example, page 32, line 18-page 33, line 8).

A Request for Corrected Filing Receipt will be filed shortly.

II. Issues regarding 35 U.S.C. §112, first paragraph—New Matter and Written Description

Claims 48 and 55-57 were rejected under 35 U.S.C. §112, first paragraph for allegedly containing new matter. Applicants respectfully disagree. Nevertheless, in an effort to advance prosecution of the subject application, and not in acquiescence of the rejection, the claims have been amended to delete the terms in question, and this rejection is now moot. In fact, on page 12 of the Office Action, the Examiner states, "The specification describes a fusion protein comprising Math1 or Hath1 and a bacterial toxin or a transduction domain on pg 10, lines 15-19, in view of pg 108, Example 22...."

Applicants respectfully request removal of the rejection.

III. Issues regarding 35 U.S.C. §112, first paragraph—Enablement

Claims 48 and 55-57 were rejected under 35 U.S.C. §112, first paragraph for allegedly lacking enablement. Applicants respectfully disagree. Nevertheless, in an effort to

advance prosecution of the subject application, and not in acquiescence of the rejection, claim 48 has been amended to recite a nucleic acid sequence encoding a fusion protein comprising a Math1 or a Hath1 amino acid sequence and an amino acid sequence comprising a receptor binding domain of a bacterial toxin or a protein transduction domain.. Applicants specification is clearly enabled for nucleic acid sequences encoding fusion proteins with Math1 or Hath1 fused to a receptor binding domain of a bacterial toxin or a protein transduction domain.

Furthermore, the Examiner states that claim 55 is not enabled because it encompasses a composition comprising two non-fused nucleic acid sequences and alleges that the specification does not teach Math1 delivered in a vector separate from a transduction domain or bacterial toxin, for example. The Examiner notes that one could have possibly made a composition comprising them separately, but that the specification allegedly does not teach how to use the composition to deliver Math1 protein to the cells and that undue experimentation would have been required.

Claim 55 has been amended to recite a composition comprising a nucleic acid sequence encoding a Math1 or a Hath1 protein in combination with a delivery vehicle, wherein the composition further comprises an additional nucleic acid sequence encoding a receptor binding domain of a bacterial toxin or a protein transduction domain. The specification of the subject application discloses vectors and associated elements (see, e.g., page 39, line 16-page 44, line 6), vector dosage and formulations (see, e.g., page 63, line 16-page 67, line 2), and transfection of cells with Math1 retroviral vectors (see, e.g., Example 21 at page 106, line 20-page 108, line 7). Moreover, disclosure of well-known techniques or scientific principles to those of skill in the art is not required. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBC v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

In addition, the specification provides ample guidance with respect to gene delivery to allow the ordinarily skilled artisan to deliver the claimed composition to a cell (see, for example, page 55, line 13, through page 58, line 20).

Thus, the instant specification provides ample guidance with respect to nucleic acid sequences, vector formulations, techniques for monitoring effective gene transfer to cells, and dosage and scheduling, which enables the ordinarily skilled artisan to make and use the invention as claimed using only routine experimentation. These teachings hold true whether for delivery of a nucleic acid molecule encoding a fusion protein, as in claim 48, or whether or not two molecules are delivered separately, as in claim 55.

In view of the above, one of ordinary skill in the art, using the instant specification as a guide, could make and use the invention at the time of filing using only routine experimentation.

For the reasons set forth above, the pending claims are enabled by the instant specification, and the rejection under Section 112, first paragraph, should be withdrawn.

IV. Issues regarding 35 U.S.C. §112, Second Paragraph

Claims 48 and 55-57 were rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claims 48 and 55, as amended, no longer utilize the term in question. Thus, the Section 112, second paragraph rejection is moot and should be withdrawn.

V. Issues regarding 35 U.S.C. §103(a)

A. Akazawa in view of Schwarze

Claims 48, 55, and 57 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Akazawa (J. Biol. Chem., 1995, Vol. 270, No. 15, pp. 8730-8738; "Akazawa") in view of Schwarze (Science, Sept. 1999, Vol. 285, pp. 1569-1572; "Schwarze"). Applicants respectfully disagree.

The Examiner fails to make a *prima facie* obviousness rejection. MPEP §2143 states that to establish a *prima facie* case of obviousness, there must be some suggestion or motivation to combine the references. There is no suggestion or motivation to combine Akazawa with Schwarze. Akazawa teaches transfer of Math1 DNA into cells for reporter

gene construct experiments to provide transcriptional analysis of Math1. As shown in Fig. 9 therein, Math1 significantly activated transcription of the tested promoter/reporter gene construct in the presence of the E box (see page 8734, col 2, first full paragraph). Therefore, the constructs generated for these experiments were obviously sufficient on their own, and there would be no motivation to attach a protein transduction domain as taught in Schwarze to the Math1 sequence. In fact, a skilled artisan would be concerned that a heterologous component such as the protein transduction domain tagged onto Math1 may affect its ability to facilitate transcription of the reporter gene and thereby interfere with the interpretations of the experiments. Therefore, there is no motivation to combine the Akazawa and Schwarze references.

Furthermore, the Examiner fails to make a *prima facie* case of obviousness by failing to identify where in Akazawa there is a suggestion to make any kind of fusion protein, including one having an HIV Tat protein transduction domain. This is particularly true given that the compositions in Akazawa were wholly adequate for their purpose and there is no indication that they were insufficient therefor. Thus, there would be no motivation to combine Akazawa with another reference to enhance delivery of an already functioning composition.

Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor. *Para-Ordnance Manufacturing, Inc. v. SGS Importers International, Inc.* 73 F.3d 1085, 37 U.S.P.Q.2d 1237 (Fed. Cir. 1995), *cert. denied*, 519 U.S. 822 (1996). To establish *prima facie* obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). There must be a teaching or suggestion to make the claimed limitations, and Applicants remind the Examiner that the level of skill in the art cannot be relied upon for suggestion. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Thus, Applicants assert that the Office has not established a *prima facie* case of obviousness to reject the claims under 35 U.S.C. §103. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, (Fed. Cir. 1991).

Akazawa does not suggest implicitly or state explicitly the utilization of Math1 as part of a fusion protein. Therefore, Akazawa would not motivate one of ordinary skill in the art to

fuse Math1 with a protein transduction domain or bacterial toxin receptor-binding domain. The compositions that were utilized were wholly suitable and the combination of Math1 with a protein transduction domain is inappropriate for the purpose needed in Akazawa.

The Examiner does not point to anywhere in Akazawa where there is motivation or suggestion to utilize a protein transduction domain,. Where applicable, the findings ***should clearly articulate which portions of the reference support any rejection***. Explicit findings on motivation or suggestion to select the claimed invention should.....be articulated in order to support a 35 U.S.C. 103 ground of rejection. *In re Dillon*, 919 F.2d at 693, 16 USPQ2d at 1901; *In re Mills*, 916 F.2d 680,683, 16 USPQ2d 1430,1433 (Fed. Cir. 1990). Obviousness can not be based on "common knowledge and common sense of a person of ordinary skill in the art without any ***specific hint or suggestion in a particular reference***." *In re Lee* 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002) (emphasis added). Given that Azakawa is silent on methods to enhance delivery, Applicants respectfully assert that the Examiner is inferring this parameter from the claimed invention, which is not permissible. The reference must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Furthermore, the person of ordinary skill in the art is an objective legal construct presumed to think along conventional lines without undertaking to innovate, whether by systematic research or by extraordinary insights. *Life Technologies, Inc. v. Clontech Laboratories, Inc.*, 224 F.3d 1320, 56 U.S.P.Q.2d 1186 (Fed. Cir. 2000), citing *The Standard Oil Co. v. American Cyanamid Company,* 774 F.2d 448, 227 U.S.P.Q. 293 (Fed. Cir. 1985), which states the following:

> The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something--call it what you will--which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under § 103 by inquiring into what patentees (i.e., inventors) would have known or would likely have done, faced with the revelations of references. ***A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate***, whether by patient, and

> often expensive, systematic research or by extraordinary insights, it makes no difference which (emphasis added).

A skilled artisan looks at the reference and does what he is told from the reference. The Examiner's allegation assumes that one of skill in the art is required to innovate, which is an improper supposition because the skilled artisan performs the methods taught or suggested therein, and the teaching of the reference is completely silent on delivery deficiencies of the Math1 reporter construct.

Therefore, there is no motivation to combine the Akazawa and Schwarze references to produce Applicants' invention, and, moreover, a skilled artisan would be required to innovate to produce the claimed composition. However, there is no inference to innovate based upon Akazawa because delivery of the compositions described therein was routine and unproblematic.

Applicants respectfully request removal of the rejection.

B. Ben-Arie in view of Schwarze

Claims 48, 55, and 57 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ben-Arie (Hum. Mol. Genet., 1996, Vol. 5, pp. 1207-1216; "Ben-Arie") in view of Schwarze (Science, Sept. 1999, Vol. 285, pp. 1569-1572; "Schwarze"). Applicants respectfully disagree.

First, Ben-Arie does not disclose transducing cells with a Math1 or Hath1 composition, which is paramount to the Examiner's argument that it would be obvious to employ a protein transduction domain. The experiments described therein are extracellular, such as genomic and cDNA library screening, which uses filter screening, *in situ* hybridization, northern analysis, and chromosomal mapping, for example.

Even if this were not true, the Examiner fails to make a *prima facie* case of obviousness, because there is no suggestion to make any kind of fusion protein in Ben-Arie, much less one having an HIV Tat protein transduction domain. Therefore, there is no motivation to employ Hath1 as a fusion protein with a protein transduction domain to enhance delivery. As such, one of skill in the art is not motivated to innovate the reagents of Applicants' invention by employing a protein transduction domain.

Applicants respectfully request removal of the rejection.

VI. Issues regarding Double Patenting

Claims 48, 55, and 57 are provisionally rejected under the judicially created doctrine of double patenting over claims 112 and 117 of co-pending Application No. 09/585,645.

Applicants submit that the Amendment and Response to Office Action filed on July 1, 2004, is fully responsive to the provisional double-patenting rejection in view of the fact that the rejection is provisional. Applicants fully and completely responded to each rejection raised by the Office and did not deliberately refrain from responding to the provisional rejection.

A "provisional rejection" is unlike a regular rejection in that it is contingent upon an event unrelated to the prosecution of the present application that may never come to pass, while a regular rejection is made in view of facts actually in existence at the time the rejection is made. A provisional double-patenting rejection is based on the claims of a co-pending application as originally filed. Because the co-pending application may never actually issue, or, alternatively, the claims as originally filed may be amended during the course of prosecution of the co-pending application such that the claims, when issued, no longer impact Applicants' claims, the rejection remains "provisional" until the co-pending application issues. If the issued application still results in a double-patenting rejection, the provisional status of the rejection is removed, and the rejection becomes a regular double-patenting rejection. Once the rejection is made non-provisional, Applicants are then able to address fully the double-patenting concerns with regard to the substance of the claims that have actually issued in the referenced patent. The Office and Applicants are saved from needless speculation as to whether the co-pending application will actually issue or what the substance of the final issued claims will be. As such, Applicants are not required to address the merits of the provisional double-patenting rejection until such time as the co-pending application actually issues.

Indeed, while M.P.E.P. § 804 allows for the merits of the rejection to be addressed while the rejection remains provisional ("[t]he merits of such a provisional rejection can be addressed by both the applicant and the examiner without waiting for the first patent to

issue"), the Court of Claims and Patent Appeals (now the Court of Appeals for the Federal Circuit) has stated: "Once the provisional rejection has been made, there is nothing the examiner and the applicant must do until the other application issues." *In re Mott*, 190 U.S.P.Q. 536, 541 (C.C.P.A. 1976) (emphasis added). M.P.E.P. § 804 allows for the prosecution to continue while a provisional double-patenting rejection is pending and even instructs the Office to continue to make such a provisional rejection until one of the applications issues as a patent. For example, M.P.E.P. § 804 states:

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

Thus, Applicants respectfully submit that the Amendment and Response to Office Action filed on July 1, 2004, was fully responsive to the provisional double-patenting rejection in view of the fact that the rejection is provisional. Applicants further submit that it is proper for the Office to continue prosecution in light of the provisional status of the rejection and to allow Applicants to address the merits of the double-patenting rejection at such time as the co-pending application actually issues.

The courts have endorsed the appropriateness of the Office allowing the provisional rejection to remain standing during prosecution until the co-pending application actually issues. For example, in *In re Wetterau*, 148 U.S.P.Q. 499 (C.C.P.A. 1966), the Court of Customs and Patent Appeals held that a provisional double-patenting rejection in view of a co-pending application was proper. Even though the claims of the co-pending application had already been allowed, the court stated, "no assurance can be given that the status will endure and a patent containing such claims will ultimately issue." 148 U.S.P.Q. at 501. The court found the uncertainty of the co-pending application's status was sufficient to allow the provisional rejection to remain standing and to prevent the applicant from having to abandon the case. In holding such, the court stated:

> If a patent were not to issue on the Carabateas [co-pending] application, the "double patenting" rejection, if here affirmed, would of necessity evaporate for the possibility of two patents would not exist. Grave injury to applicant's rights might occur if the Wetterau [applicant's] application were to go abandoned through no fault of the applicant prior to the issuance of Carabateas, the reference application.
>
> *Id.*

In view of the above, Applicants submit that they have acknowledged the provisional double-patenting rejections and, further, that it is clear Applicants are not required to address the merits of the provisional double-patenting rejections until such time as the co-pending application(s) issue and the rejections are made non-provisional. As such, Applicants have fully and completely responded to each rejection raised by the Office, and, thus, they request that the Examiner reflect this in the record.

VII. Conclusion

Applicants believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P01899US3 from which the undersigned is authorized to draw.

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Respectfully submitted,

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